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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/720,066	10/19/2001	Michael Hallek	50125/019001	8894

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EXAMINER	
MARVICH, MARIA	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 11/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/720,066	HALLEK ET AL.	
	Examiner	Art Unit	
	Maria B. Marvich, PhD	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,29-32 and 35-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,29-32,35-40,42 and 43* is/are rejected.

7)☒ Claim(s) *41* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 November 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/1/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to an amendment and request for continued examination filed 9/1/05. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/1/05 has been entered.

Claims 2-28, 33 and 34 have been cancelled. Claim 43 have been added. Claims 1, 29, 31, 35, 37, 39, 41 and 42 have been amended. Claims 1, 29-32 and 35-43 are pending in the application.

Response to Amendment

Any rejection of record in the previous action not addressed in this office action is withdrawn.

Information Disclosure Statement

An IDS filed 9/1/05 has been identified and the document considered. The signed and initialed PTO Form 1449 has been mailed with this action.

Claim Objections

Claims 31 and 36 are objected to because of the following informalities: Claim 31, line 2 recites that "the mutated structural protein brings about a change in an interaction of the

structural protein with a cell membrane receptor". However, the mutation brings about or induces a change in the interaction of the mutated structural protein with a cell membrane receptor, which is supported by the specification which teaches "the mutation causes" the change in interaction. Hence it would be remedial to recite, "wherein the mutation causes a change in interaction of the structural protein with a cell membrane receptor". **This is a new objection.**

Claim 36, line 4 recites "a single-chain antibody binding to a cell surface receptor". As recited, the claim suggests that the amino acid insertion is an antibody bound to a receptor. However, according to the specification, the insertion is actually an antibody that has the potential to bind to the receptor (see page 8). It would be remedial to recite "a single–chain antibody that binds to a cell surface receptor". Appropriate correction is required. **This is a new objection.**

Claim 41 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot reference two sets of claims of different features. See MPEP § 608.01(n). Accordingly, the claim not been further treated on the merits. **This is a new objection.**

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101, which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed.

Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 29-32, 35-40 and 42 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 121, 122, 130 and 143 of copending Application No. 10/498,163. **This is a new rejection.**

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claims because the examined claim is either anticipated by, or would have been obvious over, the reference claims. Although the conflicting claims are not identical, they are not patentably distinct from each other because the cited claims of the instant invention are generic to all that is recited in claims 121, 122, 130 and 143 of U.S. application 10/498,163. That is, the cited claims of U.S. application 10/498,163 anticipate and fall entirely within the scope of the rejected claims of the instant application. Specifically, the instant claims and U.S. 10/498,163 claims recite a structural (cap or capsid) protein and the nucleic acid coding for the structural protein with an insertion after an amino acid such as 587 (amino acid N in SEQ ID NO:7 of the instant claims). Claim 121 of US application 10/498,691 specifically recites insertion of RGD, which is a ligand that interacts with cell surface integrin receptors and is specifically designed to increase infectivity to cells as recited in claim 1 of the instant invention.

The specification of 10/498,163 teaches that the amino acid 587 recited in claim 122 is specifically from AAV2 and corresponds to N of SEQ ID NO:7 of instant claim 1. The capsid proteins VP1, VP2 and VP3 are components of AAV particles and are all encoded by the same transcript and result from alternative splicing. Instant application 10/498,163 refers to the amino acids as numbered from the N-terminus of VP-1. However, the insertion if after amino acid 587 could be in VP-3 as recited in claim 29 and 30 of the instant invention as the amino acid recited as 587 is included in VP-1, VP2 and VP-3. An insertion of an RGD ligand at 587 alters binding at the heparan sulfate receptor as taught by 10/498,163.

Additionally, if a patent resulting from the instant claims was issued and transferred to an assignee different from the assignee holding the Application No. 10/498,163, then two different assignees would hold a patent to the claimed invention of Application No. 10/498,163, and thus improperly there would be possible harassment by multiple assignees.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1, 29-32, 35-40, 42 and 43 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. **These are new rejections.**

Claims 1, 29-32, 35-40, 42 and 43 are drawn to a product that could read on a product of nature. A structural protein in nature could comprise a naturally -occurring mutation within the

structural protein that increases infectivity. In this instance, the structural protein, nucleic acid encoding it and a cell comprising the nucleic acid would be a product of nature. Therefore, the claims as written do not sufficiently distinguish over cells that exist naturally because the claims do not particularly point out any non-naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206, USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor , e.g. by insertion of "Isolated" or "Purified"

Furthermore, claim 40 is drawn to a "cell" comprising the nucleic acid of claim 39. The specification teaches that the cells can be within an organism (see page 15, line 20-31) or can be *in vitro* (see page16-21). Thus the cells can be *in vivo* and as such, the scope of the claims encompasses a human being, which is non-statutory subject matter. As such, the recitation of the limitation "non-human" or "isolated" would be remedial.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 30 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 30 and 35 are vague and indefinite in that the metes and bounds of "the insertion" are unclear. The claims are drawn to a structural protein that comprises one or more amino acid insertions. Therefore, it is unclear if by recitation of "the insertion" in claims 30 and

35 that applicants mean one of the insertions or all of the insertions should there be more than one insertion. If it were any one of the insertions it would be remedial to recite "at least one of the amino acid insertions". If it were all insertions, it would be remedial to recite "the one or more amino acid insertions". **This is a new rejections.**

Claim 35 is vague and indefinite in that the metes and bounds of the Markush group are unclear. Claim 35 is drawn to a Markush group of insertions. By use of the alternative "or" in combination with "and", it is unclear which of the types of insertions are in the alternative and which must include more than one recited type of insertion. **This is a new rejections.**

Claim 35 recites the limitation "the foreign gene" in 1. There is insufficient antecedent basis for this limitation in the claim. **This is a new rejections.**

Claim 35 is vague and indefinite in that that metes and bounds of "a signal for double-strand synthesis" are unclear. Given the art accepted meaning of "a signal", i.e. Webster online define it as a sign or indication or non-verbal communication, the nature and requirements of "a signal for double-strand synthesis" are unknown. For example, it is unclear if the signal is a sign that double-strand synthesis has occurred or is it a sequence that directs or initiates double-strand synthesis or is there some other meaning of "signal"? Given that lack of guidance in the specification the metes and bounds of "a signal for double-strand synthesis" are unclear. **This is a new rejections.**

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 29-32, 35-40, 42 and 43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicants claim a genus of structural proteins, which comprises at least one mutation, wherein the mutated structural protein comprises one or more amino acid insertion, which brings about an increase in infectivity of AAV. The amino acid insertions are located before and/or after at least one amino acid sequence found in SEQ ID NO: 2, 3, 4, 5, 6, 7 and 8, wherein the mutated structural protein is capable of particle formation. **This rejection is maintained for reasons of record in the office action filed 10/16/03, 5/18/04, 6/29/05 and restated here. The rejection has been extended to newly added claims 43.**

Applicants claim in claim 35, a protein or peptide having a "signal" for double-strand synthesis of a foreign gene. **This is a new rejection.**

The written description requirement for genus claims may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with known or disclosed correlations between function and structure, or by a combination of such characteristics sufficient to show that the applicant was in possession of the claimed genus.

The instant invention recites a structural protein of AAV2, which comprises at least one mutation wherein the mutated structural protein comprises one or more amino acid mutations that bring about an increase in infectivity. The structural protein is also capable of particle formation. The amino acid insertion is either before and/or after at least one amino acid in the sequences listed as SEQ ID NO: 2, 3, 4, 5, 6, 7 and 8. These sequences are found in AAV2 capsid proteins (see page 17, line 8-23). Furthermore, the claims are drawn to a nucleic acid coding for these structural protein as well as cells comprising the nucleic acid. As well, the claims are drawn to methods of preparing the structural proteins and use of the structural proteins to alter tropism of AAV2. The critical element of all of the claims is a structural protein comprising a mutation with one or more amino acid insertions.

The specification defines "structural proteins " as capsid proteins, which are VP1, VP2 and VP3 (see page 1, paragraph 2 and 3). These proteins are encoded by overlapping sequences of the same open reading frame leading to obligatory expression of all the capsid proteins (see page 2, line 1-10). The recited sequences within SEQ ID NO: 2, 3, 4, 5, 6, 7 and 8 represent loop structures that were identified within the capsid proteins VP1, VP2 and VP3 of AAV2 (see page 11, line 10-18). These regions were identified by comparison of the crystal structure and nucleic acid sequences of three viruses CPV, AAV2 and B19. By insertions of amino acids within the loops, applicants endeavor to modify the capsid proteins such that they are more specific and efficient gene transfer vectors (see e.g. page 5, paragraph 3).

The potential mutations are large in number and diverse for the following reasons. By recitation of "amino acid insertion(s)", the insertion can be as small as a single amino acid or as large as a gene. Secondly, there can be multiple insertions within the structural protein, which

leads to a complex and large number of possible structural proteins. For example, considering a single insertion prior to or after the recited amino acids, a collection of proteins would be generated totaling about 77. This collection would increase exponentially upon introduction of multiple mutations within the singly mutated proteins. Thirdly, the claims recite that the insertions are before and/or after the recited amino acids. As the exact location of insertion is unclear, it does not appear that the insertion need be directly following or directly prior to the recited amino acids but rather can be anywhere before and/or anywhere after the amino acid as long as the insertion is within the structural protein. As guidance, applicants have only demonstrated insertion of a laminin P1 ligand into VP1 and VP3 (pages 16-20). Specifically, Tables 1 and 2 depict five insertion mutants in which laminin P1 ligand is inserted directly following R in SEQ ID NO:4 (ins447 or I-447), directly following FF in SEQ ID NO:5 (ins534 or I-534), directly following T in SEQ ID NO: 6 (ins573 or I-573), directly following N in SEQ ID NO:7 (ins587 or I-587) and directly following T in SEQ ID NO:8 (ins713 or I-713). One viral particle that results from insertion of P1 into amino acid 587 (I-587) is shown to have increased infectivity of M07-LP1-R and B16F10 cells. Therefore, of these insertions, only one can tolerate the mutation and form particles and have increased infectivity. This mutation is at site 587 (I-587). The specification also teaches at page 28 that VP3 protein was mutated by the insertion of Z34C domain of protein A but no indication about the ability of the structural protein to form particles or increase infectivity is provided. Post filing art by Reid et al (J. Virol. 76:4559-4566, 2002, referenced in applicants' arguments filed 11/22/04) demonstrate that this insertion is, like that in the instant specification, following amino acid 587 of VP3. Applicants do not disclose any "signals" for double-strand synthesis.

The disclosure of insertion of the P1 ligand at amino acid 587 of VP3 to alter specificity to the two cell types is not accompanied by a disclosure as to the relative properties of this structural protein or a correlation between the structure of this mutation and its ability to alter infectivity. Therefore, following the guidance in the specification only a single site of insertion has been identified and that is after amino acid 587 of AAV2 VP3. Hence, there is no clear description of the structural or functional characteristics required for any other mutated structural proteins to increase infectivity. Given the large number of mutant structural proteins envisioned by the invention and the inability to determine which mutant structural proteins will increase infectivity and be capable of particle formation, it is concluded that the invention must be empirically determined. In an unpredictable art, the disclosure of a single species would not represent to the skilled artisan a representative number of species sufficient to show applicants were in possession of claimed genus. Therefore, the skilled artisan cannot envision the detailed structure of the broad class of recited AAV mutant structural proteins regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that the protein is part of the invention and a reference to a potential method for isolating it. The disclosure of a single member of this genus does not suggest that the applicant was in possession of the genus.

As to "signals" of double strand synthesis, applicants do not provide any guidance as to the selection or identification of any "signals". Hence, it is not clear what a "signal" is and if it is a sequence what structural requirements for such a signal exist. Neither the prior art nor the specification teaches any "signals" nor what function it performs for double-strand synthesis. Given the unknown nature of "signals" and the inability to determine which will also possess the

ability to function in AAV2 to increase infectivity, it is concluded that the invention must be empirically determined. In an unpredictable art, the disclosure of no species would not represent to the skilled artisan a representative number of species sufficient to show applicants were in possession of claimed genus.

Response to Arguments-35 USC § 112, 1st paragraph-written description

Applicants traverse the rejections under 35 U.S.C 112, first paragraph on pages 5-7 of the amendment filed 9/1/05. Applicants argue that the claims are now drawn to a structural protein from AAV2 that includes an insertion mutation positioned before and/or after one of 11 possible consecutive amino acid positions at 7 possible sites within the capsid protein. Applicants argue that this invention is clearly described in the specification. The expression of P1 on the capsid surface is demonstrated and the binding of AAV2 capsid insertions to integrin expressing cells as well as a P1 mutation in VP3.

Applicant's arguments filed 9/1/05 have been fully considered but they are not persuasive. Applicants have recited a broad genus of structural proteins, which comprise at least one mutation wherein the mutated structural protein comprises one or more amino acid mutations that bring about an increase in infectivity. The structural protein is also capable of particle formation. Applicants have attempted to narrow the genus of proteins by recitation that the amino acid insertion is either before and/or after at least one amino acid in the sequences listed as SEQ ID NO: 2, 3, 4, 5, 6, 7 and 8. However, the claims as recited are drawn to a broad and diverse genus of structural proteins comprising "amino acid insertion(s)". The insertion can be any insertion and without limitation can be located before and/or after the recited sequences.

Hence, the location of the insertions is quite broad. As well, any number of insertions can be made into the structural protein. Functionally, these structural proteins must exhibit an increase in infectivity and also can form particles and have altered tropism. Applicants have only demonstrated a single structural protein comprising a P1 insertion that meets the functional requirements of increased infectivity, is capable of particle formation and altered tropism. The specification lacks any guidance as to the structural requirements of this structural protein that can provide increased infectivity, alter tropism or maintain particle formation. Therefore, the specification has failed to describe the genus of proteins such that the nexus of structure and function is apparent. Given the lack of disclosure as to the structural requirements of the diverse group of recited proteins, the skilled artisan cannot envision the detailed structure of the broad class of proteins regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that the sequence is part of the invention and a reference to a potential method for isolating it. The disclosure of a single member of this genus does not suggest that the applicant was in possession of the genus.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 29-32, 35-40, 42 and 43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it

pertains, or with which it is most nearly connected, to make and/or use the invention. **This is a new rejection.**

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) **Nature of invention**. The instant claims are drawn to a structural protein of AAV2, which comprises at least one mutation wherein the mutated structural protein comprises one or more amino acid mutations that bring about an increase in infectivity. The structural protein is also capable of particle formation. As well, the claims are drawn to nucleic acids coding for the structural protein and cells comprising the nucleic acid, a process for preparation of the structural protein and methods for altering the tropism of AAV using the cell comprising nucleic acid encoding the structural protein. By insertions of amino acids within the loops, applicants endeavor to modify the capsid proteins such that they are more specific and efficient gene transfer vectors (see e.g. page 5, paragraph 3).

2) **Scope of the invention**. Specifically, the amino acid insertion(s) is (are) before and/or after at least one amino acid in the sequences listed as SEQ ID NO: 2, 3, 4, 5, 6, 7 and 8. The recited sequences within SEQ ID NO: 2, 3, 4, 5, 6, 7 and 8 represent loop structures that were identified within the capsid proteins VP1, VP2 and VP3 by comparison of the crystal structure as

well as the nucleic acid sequences of three viruses CPV, AAV2 and B19 (see page 11, line 10-18). Given the broad interpretation of before and after the recited sequences, the undefined nature of the requisite number of insertions and number of amino acids that comprise the insertion, the claims encompasses broad and diverse collection of structural proteins. The insertion is intended to be of amino acids that function to increase infectivity. For example, insertion of a ligand could decrease affinity of interaction with a native receptor and increase affinity to a non-native receptor. Hence, claim 31 recites that the structural protein has a change in "an' interaction of the structural protein with "a" cell membrane receptor. It would require undue experimentation to determine which of the structural proteins would result in an increase in infectivity of AAV that is capable of particle formation and can alter tropism of AAV2.

3) **Number of working examples and guidance**. VP1, VP2 and VP3 are encoded by overlapping sequences of the same open reading frame leading to obligatory expression of all the capsid proteins (see e.g. page 2, line 1-10). Following identification of "loop structures", applicants, as depicted in Tables 1 and 2, generate five insertion mutants in which laminin P1 ligand is inserted directly following R in SEQ ID NO:4 (I-447), directly following FF in SEQ ID NO:5 (I-534), directly following T in SEQ ID NO: 6 (I-573), directly following N in SEQ ID NO:7 (I-587) and directly following T in SEQ ID NO:8 (I-713). No further experiments were demonstrated with I-713 other than to determine its packaging efficiency. The specification teaches that two of the insertions I-447 and I-587 can form particles but the ability of I-534 and I-573 to form particles is two orders of magnitude less (table 2). P1 interacts with integrin receptor. To analyze the infectivity of the AAV2 particles resulting from the four mutations, B16F10 and RN22 cells expressing P1 specific integrin on their surface were infected with

particles produced comprising the mutant structural proteins. No binding of wild type AAV2 and I-534 and I-573 to these cells were detected. While, I-447 and I-587 were able to bind to both cells, B16F10 cells transfected with I-447 were as inefficient as wild-type cells in generating titer (table 3). Therefore, one viral particle that results from insertion of P1 into amino acid 587 (I-587) is shown to have increased infectivity of B16F10 cells. This mutant is at site 587 of AAV2 VP3. The specification also teaches at page 28 that VP3 protein was mutated by the insertion of Z34C domain of protein A but no indication about the ability of the structural protein to form particles or increase infectivity is provided. Post filing art by Reid et al (J. Virol. 76:4559-4566, 2002, referenced in applicants' arguments filed 11/22/04) demonstrate that this insertion is, like that in the instant specification, following amino acid 587 of VP3.

4) **State of Art**. AAV-2 can infect a wide variety of cell types according to Ruffing et al (page 3385, col 2, paragraph 2; applicant provided in the amendment filed 11/22/04) hence the vector has been considered a valuable tool for gene therapy for the delivery of therapeutic molecules. Mutational analysis of the AAV2 capsid proteins has been undertake to identify locations that will alter the tropism of AAV2 and hence "increase the infectivity". Despite numerous attempts to find locations that are tolerant of insertion and lead to an increase in infection, functionally relevant regions of AAV-2 did not always translate into actual sites for insertion. Buning et al (Gene Therapy, 2003, Vol 10, pages 1142-1151) review the art of targeting AAV-2 by insertion mutagenesis. According to Buning et al on page 1148, several parameters lead to the unpredictability of insertional mutagenesis (1) "surface display of a ligand alone is a prerequisite but not sufficient for a ligand-dependent infection by the virus mutant" (2) "scaffold sequences flanking the heterologous ligand are important for epitope display, (3) "Not

every ligand, even if comparable in length, is tolerated at a specific insertion site" (page 1148, col 1, (2)). Therefore, using surface locations as determination of sites for insertion of any amino acid is a highly unpredictable art. Accordingly, it is demonstrated by Buning et al that I-587 alone presents promise for receptor specific peptides (see page 1143, col 2, paragraph 2). Hence using the corresponding method of the instant invention, a single species of insertion sites has reproducibly been demonstrated.

Wu et al (JVI, 2000, Vol 74, pages 8635-8647, applicant provided in the amendment filed 11/22/04) undertook a more systemic approach to characterize the capsid protein. Wu et al teaches that the art of generating AAV2 structural proteins with mutations that exhibit increased infectivity and form particles with altered tropism is unpredictable. Wu generated 93 insertion mutants at 59 locations. Wu et al generated a functional map of the AAV2 capsid and demonstrated which sites could actually tolerate substitutions, deletions or insertions. The sites were mutated by insertion of epitopes or ligands, by alanine-scanning mutagenesis in which 2-5 amino acids are altered to alanine residues and epitope substitution mutations. In fact, Wu found that not all substitutions or insertions were the same and that regions that could tolerate alanine substitutions could not tolerate other types of substitutions and the ability to introduce FLAG into the capsid reduced or abolished particle formation (see Wu et al, page 8640, col 1-2 and table 4). Therefore, Wu et al inserted HA into loop structures, reasoning that insertion would not affect capsid assembly or stability. While 6 sites tolerated substitution, only two demonstrated altered tropism confirming that the state of the art of determining insertions sites based upon structural characteristics is highly unpredictable.

5) **Unpredictability of the art**. The instant specification suggests identifying surface located regions of the structural proteins by either comparison of sequences of several AAV serotypes or computer-assisted comparison of CPV, AAV2 and B19. Applicants then propose that utilization of these surface locations for insertional mutational would allow generation of particles that have an increase in infectivity. Applicants conclude "it is also possible likewise to introduce an insertion in to the five directly adjacent AAs located next to the bold AA, because these are likewise located within a loop in the AAV2 capsid" (page 16, line 25-28). However, applicants only demonstrate the operability of a single insertion site with a single type of amino acid insertion, a P1 ligand, that leads to increased infectivity of P1 receptor containing cells thus altering the tropism of this vector. Given the broad nature of the recited structural proteins and the unknown nature of the amino acid insertion and the unknown numbers of insertions, the invention has a high level of unpredictability. The MPEP teaches, "However, claims reading on significant numbers of inoperative embodiments would render claims non-enabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. Atlas Powder Co. v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); In re Cook, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971). (see MPEP 2164.08(b). As taught by Buning et al, it is highly unpredictable that demonstration of a surface loop will itself provide the functional characteristics for altered tropism or increased infectivity. Furthermore, the demonstration that P1 functions at I-587 to increase infectivity to B16F10 does not provide adequate teachings that any ligand in any site will also provide the recited functional characteristics. Finally, the ability to determine *a priori* the functional aspects of a protein based upon primary amino acid sequence

is poorly established in the art. For example, Tseng and Liang teach that protein surfaces in particle experience very different selective pressure than other functional domains and global protein sequence and structure similarity are often unreliable for function prediction (see Introduction). Smith and Zhang provide teachings that confirm that inconsistencies and outright errors are encountered when assigning probable function to sequences (see page 1222, col 2, paragraph 1).

6) **Summary**. The invention recites a structural protein of AAV2, which comprises at least one mutation wherein the mutated structural protein comprises one or more amino acid mutations that bring about an increase in infectivity. The structural protein is also capable of particle formation. Given the broad interpretation of before and after the recited sequences, the undefined nature of the requisite number of insertions and number of amino acids that comprise the insertion, the claims encompasses broad and diverse collection of structural proteins. It would require undue experimentation to determine which of the structural proteins would result in an increase in infectivity of AAV and is capable of particle formation with altered tropism.

In view of predictability of the art to which the invention pertains and the lack of guidance in the specification: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue unpredictable experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 29, 31, 32, 35-40, 42 and 43 are rejected under 35 U.S.C. 102(a) as being anticipated by Mamounas et al (WO 97/38723 publication date October 23, 1997 (provided by applicant), see entire document). **Upon reconsideration, this rejection has been extended to claim 1, which incorporates limitations from now cancelled claim 14, previously not included in the rejection mailed 6/29/05. Hence this is a new rejection.**

Mamounas et al teach a structural protein comprising a mutation at the N-terminus of AAV2 VP-1, VP-2 or VP-3 in which targeting peptides are inserted (see e.g. page 61, line 33-35, page 67, line 24-26, page 69, line 11-14 and line 15-26 and table 3). The instant claims do not limit the location of the insertions beyond describing that the insertions are before and/or after one of the amino acids in SEQ ID NO: 2, 3, 4, 5, 6, 7 and 8. Therefore the occurrence of an insertion at the N-terminus of VP1, VP2 and VP3 places the insertion before many of the amino acids recited in claim 1 such that Mamounas et al anticipate all that is recited in claims 1, 29 and 43. Resultant particles comprising the mutated structural protein as part of the capsid demonstrate reduced binding at the wild-type receptor 150 kD heparan sulphate proteoglycan receptor (see e.g. page 3, line 9-15) as recited in claims 31, 32, 37 and 38. The insertion within the structural protein of Mamounas et al comprises a ligand (see e.g. page 43, line 28-30) as recited in claim 35. Claim 35 is interpreted for purposes of this art rejection to comprise a

Markush listing of single potential insertions into the structural protein. Furthermore, the ligand can be a C4 peptide, which can bind via its charge or type of amino acid or monoclonal antibody single chain fragments (see e.g. page 17, line 30 through page 19, line 10) as recited in claim 36. Nucleic acid comprising the structural protein is used to generate rAAV within HeLa and is part of the capsid and hence part of the particle (see e.g. page 68, line 19-31) as recited in claims 37-41. The resultant particle has altered tropism (see e.g. page 69, line 15-26) as recited in claim 42. Therefore, Mamounas et al anticipate claims 1, 29, 31, 32, 35-40, 42 and 43.

Response to Arguments-35 USC § 102

Applicants traverse the rejections under 35 U.S.C 102, first paragraph on page 7 of the amendment filed 9/1/05. Applicants argue that the claims as amended overcome the rejection under 35 USC 102 as being anticipated by Mamounas et al .

Applicant's arguments filed 9/1/05 have been fully considered but they are not persuasive. Upon reconsideration of the claims, the prior art rejection of the instant claims has been extended to limitations of claim 14 now incorporated into claim 1. The broadest interpretation of insertion sites that are before and/or after the recited SEQ ID NO:s include locations that are distinct from the recited amino acids. Accordingly, Mamounas by teaching insertions at the N-terminus of Vp1, Vp2 and Vp3 teach a variety of structural proteins comprising insertions before most of the recited amino acids.

Conclusion

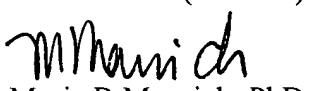
Claims 1, 29-32, 35-40, 42 and 43 are rejected.

Claim 41 is objected to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, David Nguyen, PhD can be reached on (571)-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Maria B Marvich, PhD
Examiner
Art Unit 1633

October 28, 2005